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Preparation of optically active 2-amino-, 2-chloro-, 2-hydroxy- or 2-alkoxy-1-alcohols

5 The present invention relates to an improved process for preparing optically active 2-amino-, 2-chloro-, 2-hydroxy- or 2-alkoxy-1-alcohols by catalytically hydrogenating optically active 2-amino-, 2-chloro-, 2-hydroxy- or 2-alkoxycarboxylic acids or their acid derivatives.

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As disclosed by EP-A-696 575 and EP-A-717 023, optically active 2-aminocarboxylic acids and 2-hydroxycarboxylic acids can be hydrogenated to optically active 2-amino-1-alkanols and 1,2-alkanediols in the presence of ruthenium catalysts such as

15 elemental ruthenium, ruthenium oxides and hydroxides or ruthenium on supports. In a reaction between 80 and 100°C, an enantiomeric excess of up to 98.5% e.e. is maintained.

According to WO 99/38838, the yields and enantiomeric excesses of 20 2-amino-1-alkanols can also be increased by hydrogenating the corresponding 2-aminocarboxylic acids in the presence of mineral acids and ruthenium catalysts which comprise from one to two further elements of atomic number from 23 to 82. Particular preference is given to ruthenium/rhenium catalysts whose use 25 leads to the retention of enantiomeric excesses of up to 99.9% e.e.

According to WO 99/38824, it is also possible to increase the yields and enantiomeric excesses of 1,2-alkanediols by using 30 ruthenium catalysts which comprise one or two further elements of atomic numbers from 23 to 82. Particular preference is given to the addition of rhenium.

WO 99/38613 describes a process for preparing particularly 35 advantageous catalysts which comprise ruthenium and at least one other element of atomic number from 23 to 82 and their use for hydrogenations. The process comprises combining a slurry of a ruthenium compound which has a specific surface area of from 50 to 300 m²/g with a solution of at least one metal compound. 40 Particular preference is given to unsupported ruthenium/rhenium catalysts which are used for the preparation of optically active 2-aminoalcohols or 1,2-diols.

It is also known that optically active 2-amino- and 45 2-hydroxycarboxylic esters can be hydrogenated at 25°C and 100 bar of hydrogen pressure in the presence of catalysts consisting of rhodium and platinum and a solvent to corresponding optically

active 2-aminoalcohols or 1,2-diols with enantiomeric excesses of over 99.9% e.e. (M. Studer et al., *Adv. Synth. Catal.* **2001**, 343, pages 802-808).

5 WO 98/52891 discloses the hydrogenation of aliphatic carboxylic acids, anhydrides, esters or lactones in the presence of platinum/rhenium catalysts which comprise a further element such as molybdenum, silver or palladium to the corresponding alcohols. This allows corrosion problems to be avoided.

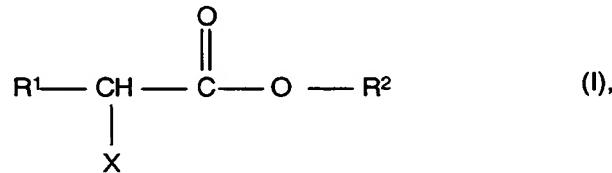
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It is an object of the present invention to provide an improved process for hydrogenating optically active 2-amino-, 2-chloro-, 2-hydroxy- and 2-alkoxycarboxylic acids and their acid derivatives to the corresponding optically active alcohols. The 15 catalysts to be used for the hydrogenation should be easy to prepare, have a high activity and lead to high yields of productive value and enantiomeric excesses.

We have found that this object is achieved by a process for 20 preparing optically active 2-amino-, 2-chloro-, 2-hydroxy- or 2-alkoxy-1-alkanols by catalytically hydrogenating appropriate optically active 2-amino-, 2-chloro-, 2-hydroxy- and 2-alkoxycarboxylic acids or their acid derivatives, which comprises carrying out the hydrogenation in the presence of 25 catalysts comprising palladium and rhenium or platinum and rhenium.

In the process according to the invention, it is possible to use, for example, optically active carboxylic acids or their 30 derivatives of the formula I

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where the radicals are defined as follows:

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R^1 : straight-chain or branched $\text{C}_1\text{-C}_{12}$ -alkyl, $\text{C}_7\text{-C}_{12}$ -aralkyl or $\text{C}_6\text{-C}_{10}$ -aryl, each of which may be substituted by NR^3R^4 , OH , COOH and/or further groups stable under the reaction conditions,

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R²: hydrogen, straight-chain or branched C₁-C₁₂-alkyl or C₃-C₈-cycloalkyl,

X: chlorine, NR⁵R⁶ or OR⁷,

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R³, R⁴, R⁵ and R⁶:

each independently hydrogen, straight-chain or branched C₁-C₁₂-alkyl, C₇-C₁₂-aralkyl, C₆-C₁₀-aryl, C₃-C₈-cycloalkyl or C₃-C₈-cycloalkyl in which one CH₂ group is replaced by O or

10 NR⁸,

R³ and R⁴ and also R⁵ and R⁶:

also each independently together -(CH₂)_m-, where m is an integer from 4 to 7,

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R¹ and R⁵:

also together -(CH₂)_n- where n is an integer from 2 to 6,

R⁷: hydrogen, straight-chain or branched C₁-C₁₂-alkyl or

20 C₃-C₈-cycloalkyl,

R¹ and R⁷:

also together -(CH₂)_n-, where n is an integer from 2 to 6 and

25 R⁸: hydrogen, straight-chain or branched C₁-C₁₂-alkyl, C₇-C₁₂-aralkyl or C₆-C₁₀-aryl,

or their acid anhydrides and hydrogenate them to the corresponding optically active alcohols.

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The R¹ radicals may be widely varied and also bear, for example, from 1 to 3 substituents stable under the reaction conditions, such as NR³R⁴, OH and/or COOH.

35 Examples of R¹ radicals include:

C₁-C₆-alkyls such as methyl, ethyl, propyl, 1-methylethyl, butyl, 1-methylpropyl, 2-methylpropyl, 1,1-dimethylethyl, pentyl, 1-methylbutyl, 2-methylbutyl, 3-methylbutyl, 2,2-dimethylpropyl,

40 1-ethylpropyl, hexyl, 1,1-dimethylpropyl, 1,2-dimethylpropyl, 1-methylpentyl, 2-methylpentyl, 3-methylpentyl, 4-methylpentyl, 1,1-dimethylbutyl, 1,2-dimethylbutyl, 1,3-dimethylbutyl, 2,2-dimethylbutyl, 2,3-dimethylbutyl, 3,3-dimethylbutyl, 1-ethylbutyl, 2-ethylbutyl, 1,1,2-trimethylpropyl,

45 1,2,2-trimethylpropyl, 1-ethyl-1-methylpropyl or 1-ethyl-2-methylpropyl,

C₁-C₁₂-alkyl such as C₁-C₆-alkyl (mentioned above) or unbranched or branched heptyl, octyl, nonyl, decyl, undecyl or dodecyl,

C₇-C₁₂-aralkyls such as phenylmethyl, 1-phenylethyl 2-phenylethyl, 5 1-phenylpropyl, 2-phenylpropyl or 3-phenylpropyl,

C₆-C₁₀-aryls such as phenyl, naphthyl or anthracenyl, each of which may bear a substituent such as NR⁹R¹⁰, OH and/or COOH.

10 Examples of definitions of R² include the following:

hydrogen, straight-chain or branched C₁-C₁₂-alkyl (as specified above) or C₃-C₈-cycloalkyl, e.g. cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl and cyclooctyl.

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Instead of the carboxylic ester, it is also possible to use acid anhydrides as carboxylic acid derivatives.

The X radical is chlorine, NR⁵R⁶ or OR⁷ where R⁵ and R⁶, exactly

20 like R³ and R⁴, or R⁹ and R¹⁰, are each independently hydrogen, straight-chain or branched C₁-C₁₂-alkyl, especially C₁-C₆-alkyl, C₇-C₁₂-aralkyl or C₆-C₁₀-aryl, especially phenyl, or C₃-C₈-cycloalkyl (each as specified above for the R¹ and R² radicals).

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The R³ and R⁴, R⁵ and R⁶, and also R⁹ and R¹⁰ pairs may each be independently combined to form -(CH₂)_m where m is an integer from 4 to 7, in particular 4 or 5. A CH₂ group may be replaced by O or NR⁸.

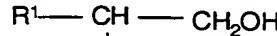
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The R¹ and R⁵ radicals may also together be -(CH₂)_n- where n is an integer from 2 to 6.

The R⁷ radical is preferably hydrogen or straight-chain or

35 branched C₁-C₁₂-alkyl or C₃-C₈-cycloalkyl, more preferably methyl, ethyl, 1-methylethyl, 1,1-dimethylethyl, hexyl, cyclohexyl or dodecyl. It may also be -(CH₂)_n- together with R¹ where n is an integer from 2 to 6.

40 The hydrogenation according to the invention provides the corresponding optically active alcohols of the formula II



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where R¹ and X are each as defined above.

Examples of useful starting materials include 2-amino-, 2-chloro-, 2-hydroxy- or 2-alkoxycarboxylic acids and their 5 derivatives where the R¹ radical, as long as it is inert under the reaction conditions, may be widely varied as described above.

Owing to the easy accessibility, preference is given to using 2-amino acids of the formula I such as phenylalanine, threonine, 10 glutamic acid, proline, aspartic acid, alanine, ornithine, valine, leucine and isoleucine and their derivatives, and also 2-hydroxy- and 2-chlorocarboxylic acids such as tartaric acid, lactic acid, 2-chloropropionic acid and malic acid and derivatives thereof.

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The catalysts used for the process according to the invention comprise palladium and rhenium or platinum and rhenium. They may be used for the hydrogenation according to the invention with or without catalyst support. They may additionally comprise at least 20 one further element having an atomic number of from 23 to 82.

Further elements for this purpose include titanium, vanadium, chromium, manganese, iron, cobalt, nickel, copper, zinc, zirconium, molybdenum, silver, tin, tungsten, lead, lanthanum and 25 cerium, preferably silver, tungsten, molybdenum and tin, more preferably silver and tin.

The weight ratio of platinum or palladium to rhenium is preferably from 100:1 to 0.01:1, more preferably from 50:1 to 30 0.05:1, in particular from 10:1 to 0.1:1. The weight ratio of platinum or palladium to the at least one further element is preferably from 100:1 to 10:1, more preferably from 50:1 to 20:1.

The catalysts used according to the invention may comprise 35 palladium, platinum, rhenium and any additional elements in different forms, for example in elemental form, in the form of compounds of palladium, platinum, rhenium and the additional elements or in the form of an intermetallic compound of palladium, platinum, rhenium and the additional elements.

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The catalyst may be used as an unsupported or supported catalyst. When it is used as a supported catalyst, the support material may be any suitable material, for example carbons, carbon blacks, graphites, silicon carbides, silicon dioxides, silicates, 45 zeolites, titanium dioxide, zirconium dioxide and aluminas. These supported catalysts may comprise, for example, from 1 to 50% by weight of metal in elemental form or in the form of compounds. A

particularly preferred support material is activated carbon pretreated oxidatively or with mineral acid. The preparation of such catalysts is described, for example, in EP-A-848 991 and US 5 698 749.

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If not applied to a support material, the catalysts may be used, for example, in colloidal form or as a finely divided solid in the manner according to the invention. Examples of catalysts include finely divided palladium/rhenium, platinum/rhenium, palladium/rhenium/silver, platinum/rhenium/silver, palladium/rhenium/molybdenum, platinum/rhenium/tungsten, platinum/rhenium/tin particles, for example in metallic form or in the form of their oxides, hydroxides, halides, nitrates, carboxylates, acetylacetones or as amine complexes.

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Particular preference is given to unsupported bimetallic palladium/rhenium or platinum/rhenium catalysts. These may also additionally comprise at least one further element of atomic number from 23 to 82. They may be prepared, for example, by reduction of mixtures of platinum oxide or palladium oxide and rhenium oxide with a reducing agent, for example hydrogen. A third metal may be deposited in the preparation of the catalyst or in situ, during the hydrogenation reaction. The preparation of such catalysts is described, for example, in WO 98/52891.

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In a preferred embodiment of the process according to the invention, the above-described optically active starting materials are hydrogenated in the presence of an organic or inorganic acid. In general, the addition of acid is from 0.5 to 1.5 equivalents, more preferably from 1 to 1.3 equivalents, based on 1 equivalent of any basic group present in the starting materials. Examples of useful organic acids include acetic acid, propionic acid and adipic acid. Preference is given to adding inorganic acids, especially sulfuric acid, hydrochloric acid and phosphoric acid. The acids may be used, for example, as such, in the form of aqueous solutions or in the form of their separately prepared salts with the starting materials to be hydrogenated, for example as sulfates, hydrogensulfates, hydrochlorides, phosphates, mono- or dihydrogenphosphates.

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Based on 1 mol of optically active starting compound used, it is possible to use, for example, from 0.1 to 10 g of the catalysts used according to the invention comprising platinum or palladium, rhenium and optionally additional metals or from 1 to 50 g of the supported catalysts.

In general, the process according to the invention is carried out in the presence of a solvent for the optically active starting materials of the formula I. Examples of useful solvents include water, water-miscible organic solvents and mixtures of both.

5 Useful water-miscible solvents include lower alcohols having from 1 to 4 carbon atoms and water-miscible ethers, e.g. tetrahydrofuran or dioxane. Preferred solvents are water and mixtures which comprise water and lower alcohols and/or tetrahydrofuran.

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The process according to the invention may be carried out, for example, at temperatures in the range from 30 to 140°C and pressures in the range from 5 to 300 bar. Preference is given to temperatures from 50 to 130°C and pressures from 10 to 280 bar.

15 Particular preference is given to temperatures from 60 to 120°C and pressures from 50 to 250 bar.

The reaction is over when no more hydrogen is taken up. Typically, the hydrogenation time is from 0.5 to 8 hours.

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To work up the reaction mixture, it may, for example, be initially cooled, the catalyst may be removed, for example by filtration, and the volatile constituents present such as solvent and water of reaction may be partly or fully removed by

25 distillation, optionally under reduced pressure. In the case of 2-aminocarboxylic acids as starting compounds, it is possible to release the aminoalcohol from its salt from the residue with base, e.g. aqueous alkali metal hydroxide solution or alcoholic alkoxide solution, remove the precipitated salt and fractionate 30 the filtrate under reduced pressure. Like the solvent, the catalyst removed can be reused.

The process according to the invention may be carried out continuously, semicontinuously or batchwise.

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Examples:

General hydrogenation procedure:

40 In a metal autoclave, 0.1 g of PtO₂ and 0.2 g of Re₂O₇, suspended in 9 g of water, are initially charged and compressed with 60 bar of hydrogen. The suspension is stirred at 270°C for 1 hour and decompressed after cooling, and 1 g of the compound to be hydrogenated is added. Hydrogenation is then effected under the 45 conditions specified below.

Inventive examples 1 to 3: Preparation of (S)-leucinol

In accordance with the procedure given, 1 g of enantiomerically pure (L)-leucine (99.9% e.e.) was hydrogenated together with 5 0.5 g of concentrated sulfuric acid. The reaction conditions are summarized in Table 1:

10	Inv.	Pressure	Temperature	Reaction time
	example	[bar]	[°C]	[h]
	1	100	60	5
	2	100	80	5
	3	100	100	5

Table 1

15 To determine the enantiomeric excesses, samples of the reaction effluents were neutralized with sodium hydrogencarbonate, trifluoroacetylated and subsequently analyzed by means of gas chromatography using a chiral Cyclodex GTA column. The 20 enantiomeric excesses in all three examples were determined to be greater than 99% e.e.

Inventive example 4: Preparation of (S)-1,2-propanediol

25 In accordance with the procedure given above, 1 g of enantiomerically pure (L)-lactic acid (99.9% e.e.) was hydrogenated at a temperature of 80°C and 200 bar of hydrogen pressure for 5 hours.

30 The enantiomeric excess of the reaction effluent was determined by means of gas chromatography using a Chirasil-Dex capillary to be greater than 99% e.e.

Inventive example 5: Preparation of S-1,2,4-butanetriol

35 A metal autoclave was initially charged with a suspension of 1.6 g of PtO₂ and 4 g of Re₂O₇ in 50 g of water which was pressurized with 60 bar of hydrogen and stirred at 270°C and 124 bar for 1 hour. After cooling, the mixture was decompressed, 40 g of L(-)-malic acid in 100 ml of water were added and hydrogenation was subsequently effected at 100°C and a pressure of 250 bar for 12 hours. S-1,2,4-butanetriol was obtained in a yield of 40.8% and with an enantiomeric excess of 97.2% e.e.

45 Inventive example 6: Preparation of S-alaninol

A metal autoclave was initially charged with a suspension of

0.4 g of PtO₂ and 1 g of Re₂O₇ in 50 g of water which was pressurized with 60 bar of hydrogen and stirred at 270°C and 125 bar for 1 hour. After cooling, the mixture was decompressed, 24 g of L-alanine and 13.8 g of concentrated sulfuric acid in 100 ml 5 of water were added and hydrogenation was subsequently effected at 60°C and a pressure of 200 bar for 12 hours. At a conversion of 14%, alaninol was obtained with an enantiomeric excess of 99.4% e.e.

10 Comparative example 1: Hydrogenation of enantiomerically pure (L)-lactic acid without Re₂O₇

Inventive example 4 was carried out under the given reaction conditions but with the omission of 0.2 g of Re₂O₇. The gas 15 chromatography analysis showed that only about 1% of the (L)-lactic acid had been converted to 1,2-propanediol.

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